

WHAT IS CLAIMED IS:

- 1 1. A composition of matter comprising a linked plurality of molecules
2 which specifically bind to the mammalian target of rapamycin (mTOR).
- 1 2. A composition of matter as in claim 1, wherein the molecules are
2 selected from the group consisting of rapamycin, rapamycin hybrids, CCI-779, RAD-001,
3 SDZ Rad (Everolimus), FK506 (Tacrolimus), ASM 981 (Pimecrolimus), Wortmannin, and
4 Tumistatin.
- 1 3. A composition as in claim 2, having from 3 to 10^6 molecules linked.
- 1 4. A composition as in claim 3, having from 5 to 10^5 molecules linked.
- 1 5. A composition as in claim 4, having from 7 to 5×10^4 molecules
2 linked.
- 1 6. A composition of matter as in any of claim 1, wherein the molecules
2 are linked via attachment to a backbone.
- 1 7. A composition of matter as in claim 6, wherein the molecules comprise
2 rapamycin molecules which have been derivatized with linking moieties and wherein the
3 rapamycin molecules are covalently bound through the moieties to the backbone.
- 1 8. A composition of matter as claim 7, wherein the linking moieties are
2 bound to the rapamycin molecules at sites which do not sterically interfere with the active
3 sites of rapamycin so that rapamycin retains its activity when attached to the backbone.
- 1 9. A composition of matter as in claim 7, wherein the linking moieties are
2 bound to the rapamycin molecules at sites which sterically interfere with the active sites of
3 rapamycin so that rapamycin activity is inhibited while the rapamycin remains attached to the
4 backbone and restored when the rapamycin is released from the backbone.
- 1 10. A composition of matter as in claim 6, wherein the backbone degrades
2 under preselected conditions to release the rapamycin molecules.
- 1 11. A composition of matter as in claim 7, wherein the linking moieties
2 lyse under preselected conditions to release the rapamycin molecules from the backbone.

1 12. A composition of matter as in claim 7, wherein the backbone
2 comprises a poly (amino acid).

1 13. A composition of matter as in claim 12, wherein the backbone is
2 polyaspartate, wherein rapamycin is covalently attached via an ester linkage between a free
3 carboxylic acid on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.

1 14. A composition of matter as in claim 12, wherein the backbone is
2 polylysine, wherein rapamycin is covalently attached via a heterobifunctional linker between
3 a free thiol on the lysine to a free hydroxyl at position 42 of rapamycin.

1 15. A composition of matter as in claim 12, wherein the backbone is
2 polylysine, wherein rapamycin is covalently attached via an amide-ester linkage between a
3 free amine on the lysine to a free hydroxyl at position 42 of rapamycin.

1 16. A composition of matter as in claim 12, wherein the backbone is
2 polylysine, wherein rapamycin is covalently attached via a disulfide linkage through a free
3 thiol introduced to the rapamycin.

1 17. A composition of matter as in claim 6, wherein the backbone
2 comprises polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to
3 the PEG by ester linkages between free hydroxyls on the PEG and on the rapamycin.

1 18. A composition of matter as in any of claim 1, wherein the molecules
2 are polymerized.

1 19. A composition of matter as in claim 18, wherein the molecules
2 comprise rapamycin molecules which have been derivatized with linking moieties and
3 wherein the rapamycin molecules are polymerized through the linking moieties.

1 20. A composition of matter as in claim 19, wherein the linking moieties
2 are bound to the rapamycin molecules at sites which do not sterically interfere with the active
3 sites of rapamycin so that rapamycin retains its activity when polymerized.

1 21. A composition of matter as in claim 19, wherein the linking moieties
2 are bound to the rapamycin molecules at sites which sterically interfere with the active sites

3 of rapamycin so that rapamycin activity is inhibited while the rapamycin remains
4 polymerized and restored when the rapamycin is released.

1 22. A composition of matter as in claim 19, wherein the linking moieties
2 lyse under preselected conditions.

1 23. A composition of matter as in claim 19, wherein the linking moieties
2 comprise ascorbic acid attached to the rapamycin molecules via an ester linkage.

1 24. An implantable prosthesis comprising:
2 a structure having a surface; and
3 linked pluralities of molecules which specifically bind to the mammalian
4 target of rapamycin (mTOR) present on the surface.

1 25. An implantable prosthesis as in claim 24, wherein the structure
2 comprises a vascular prosthesis or stent implantable in a blood vessel.

1 26. An implantable prosthesis as in claim 24, wherein the linked pluralities
2 are covalently attached to the surface.

1 27. An implantable prosthesis as in claim 24, wherein the linked plurality
2 of molecules comprise molecules which are selected from the group consisting of rapamycin,
3 rapamycin hybrids, CCI-779, RAD-001, SDZ Rad (Everolimus), FK506 (Tacrolimus), ASM
4 981 (Pimecrolimus), Wortmannin, and Tumistatin.

1 28. An implantable prosthesis as in claim 27, having from 3 to 10^6
2 molecules linked.

1 29. An implantable prosthesis as in claim 28, having from 5 to 10^5
2 molecules linked.

1 30. An implantable prosthesis as in claim 29, having from 7 to 5×10^4
2 molecules linked.

1 31. An implantable prosthesis as in any of claim 24, wherein the molecules
2 are linked via attachment to a backbone.

1 32. An implantable prosthesis as in claim 31, wherein the molecules
2 comprise rapamycin molecules which have been derivatized with linking moieties and
3 wherein the rapamycin molecules are covalently bound through the moieties to the backbone.

1 33. An implantable prosthesis as claim 32, wherein the linking moieties
2 are bound to the rapamycin molecules at sites which do not sterically interfere with the active
3 sites of rapamycin so that rapamycin retains its activity when attached to the backbone.

1 34. An implantable prosthesis as in claim 32, wherein the linking moieties
2 are bound to rapamycin molecules at sites which sterically interfere with the active sites of
3 rapamycin so that rapamycin activity is inhibited while the rapamycin remains attached to the
4 backbone and restored when the rapamycin is released from the backbone.

1 35. An implantable prosthesis as in claim 31, wherein the backbone
2 degrades under preselected conditions to release the rapamycin molecules.

1 36. An implantable prosthesis as in claim 32, wherein the linking moieties
2 lyse under preselected conditions to replace the rapamycin molecules from the backbone.

1 37. An implantable prosthesis as in claim 32, wherein the backbone
2 comprises a poly (amino acid).

1 38. An implantable prosthesis as in claim 37, wherein the backbone is
2 polyaspartate, wherein rapamycin is covalently attached via an ester linkage between a free
3 carboxylic acid on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.

1 39. An implantable prosthesis as in claim 37, wherein the backbone is
2 polylysine, wherein rapamycin is covalently attached via a heterobifunctional linker between
3 a free thiol on the lysine to a free hydroxyl at position 42 of rapamycin.

1 40. An implantable prosthesis as in claim 37, wherein the backbone is
2 polylysine, wherein rapamycin is covalently attached via an amide-ester linkage between a
3 free amine on the lysine to a free hydroxyl at position 42 of rapamycin.

1 41. An implantable prosthesis as in claim 37, wherein the backbone is
2 polylysine, wherein rapamycin is covalently attached via a disulfide linkage through a free
3 thiol introduced to the rapamycin.

1 42. An implantable prosthesis as in claim 31, wherein the backbone
2 comprises polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to
3 the PEG by ester linkages between free hydroxyls on the PEG and on the rapamycin.

1 43. An implantable prosthesis as in any of claim 24, wherein the molecules
2 are polymerized.

1 44. An implantable prosthesis as in claim 43, wherein the molecules
2 comprise rapamycin molecules which have been derivatized with linking moieties and
3 wherein the rapamycin molecules are polymerized through the linking moieties.

1 45. An implantable prosthesis as in claim 44, wherein the linking moieties
2 are bound to the rapamycin molecules at sites which do not sterically interfere with the active
3 sites of rapamycin so that rapamycin retains its activity when polymerized.

1 46. An implantable prosthesis as in claim 44, wherein the linking moieties
2 are bound to the rapamycin molecules at sites which sterically interfere with the active sites
3 of rapamycin so that rapamycin activity is inhibited while the rapamycin remains
4 polymerized and restored when the rapamycin is released.

1 47. An implantable prosthesis as in claim 44, wherein the linking moieties
2 lyse under preselected conditions.

1 48. An implantable prosthesis as in claim 44, wherein the linking moieties
2 comprise ascorbic acid attached to the rapamycin molecules via an ester linkage.

1 49. A method for preparing a linked plurality of molecules which
2 specifically bind to the mammalian target of rapamycin (mTOR), said method comprising:
3 providing a backbone molecule; and
4 binding the plurality of molecules to the backbone molecule.

1 50. A method as in claim 49, wherein the molecules are selected from the
2 group consisting of rapamycin, rapamycin hybrids, CCI-779, RAD-001, SDZ Rad
3 (Everolimus), FK506 (Tacrolimus), ASM 981 (Pimecrolimus), Wortmannin, and Tumistatin.

1 51. A method as in claim 50, wherein the plurality consists of from 3 to
2 10^6 molecules.

1 52. A method as in claim 51, wherein the plurality consists of from 5 to
2 10^5 molecules.

1 53. A method as in claim 52, wherein the plurality consists of from 7 to
2 5×10^4 molecules.

1 54. A method as in any of claim 49, wherein the molecules comprise
2 rapamycin molecules which have been derivatized with linking moieties and wherein the
3 rapamycin molecules are covalently bound through the moieties to the backbone.

1 55. A method as in claim 54, wherein the linking moieties are bound to the
2 rapamycin molecules at sites which do not sterically interfere with the active sites of
3 rapamycin so that rapamycin retains its activity when attached to the backbone.

1 56. A method as in claim 54, wherein the linking moieties are bound to
2 rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so
3 that rapamycin activity is inhibited while the rapamycin remains attached to the backbone
4 and restored when the rapamycin is released from the backbone.

1 57. A method as in claim 54, wherein the backbone degrades under
2 preselected conditions to release the rapamycin molecules.

1 58. A method as in claim 54, wherein the linking moieties lyse under
2 preselected conditions to release the rapamycin molecules from the backbone.

1 59. A method as in claim 54, wherein the backbone comprises a poly
2 (amino acid).

1 60. A method as in claim 59, wherein the backbone is polyaspartate,
2 wherein rapamycin is covalently attached via an ester linkage between a free carboxylic acid
3 on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.

1 61. A method as in claim 59, wherein the backbone is polylysine, wherein
2 rapamycin is covalently attached via a heterobifunctional linker between a free thiol on the
3 lysine to a free hydroxyl at position 42 of rapamycin.

1 62. A method as in claim 59, wherein the backbone is polylysine, wherein
2 rapamycin is covalently attached via an amide-ester linkage between a free amine on the
3 lysine to a free hydroxyl at position 42 of rapamycin.

1 63. A method as in claim 59, wherein the backbone is polylysine, wherein
2 rapamycin is covalently attached via a disulfide linkage through a free thiol introduced to the
3 rapamycin.

1 64. A method as in claim 59, wherein the backbone comprises
2 polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to the PEG
3 by ester linkages between free hydroxyls on the PEG and on the rapamycin.

1 65. A method for preparing a linked plurality of molecules which
2 specifically bind to the mammalian target of rapamycin, said method comprising:
3 polymerizing the molecules.

1 66. A method as in claim 65, wherein the plurality consists of from 3 to
2 10^6 molecules.

1 67. A method as in claim 66, wherein the plurality consists of from 5 to
2 10^5 molecules.

1 68. A method as in claim 67, wherein the plurality consists of from 7 to
2 5×10^4 molecules.

1 69. A method as in claim 65, wherein the molecules comprise rapamycin.

1 70. A method as in claim 69, wherein polymerizing comprises:
2 derivatizing the rapamycin molecules with a polymerizable moiety; and
3 polymerizing the polymerizable moieties to covalently bind the rapamycin
4 molecules via the moieties.

1 71. A method as in claim 70, wherein the linking moieties are bound to the
2 rapamycin molecules at sites which do not sterically interfere with the active sites of
3 rapamycin so that rapamycin retains its activity when polymerized.

1 72. A method as in claim 70, wherein the linking moieties are bound to the
2 rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so
3 that rapamycin activity is inhibited while the rapamycin remains polymerized and restored
4 when the rapamycin is released.

1 73. A method as in claim 70, wherein the polymerized moieties lyse under
2 preselected conditions.

1 74. A method as in claim 70, wherein the polymerized moieties comprise
2 ascorbic acid attached to the rapamycin molecules via an ester linkage.

1 75. A method as in claim 70, wherein the polymerizable moiety comprises
2 ascorbic acid.

1 76. A method for modifying an implantable prosthesis, said method
2 comprising:
3 providing an implantable prosthesis having a surface; and
4 binding linked pluralities of molecules which specifically bind to the
5 mammalian target of rapamycin (mTOR).

1 77. A method as in claim 77, wherein the implantable prosthesis comprises
2 a vascular prosthesis or stent implantable in a blood vessel.

1 78. A method as in claim 77, wherein binding comprises covalently
2 attaching linked pluralities of rapamycin to the surface.

1 79. A method as in claim 78, wherein binding comprises generating free
2 amines on the surface and forming an amide linkage to a carboxy moiety in the linked
3 pluralities of rapamycin.

1 80. A method as in claim 78, wherein the linked pluralities of rapamycin
2 have from 3 to 10^6 molecules linked.

1 81. A method as in claim 79, wherein the linked pluralities of rapamycin
2 have from 5 to 10^5 molecules linked.

1 82. A method as in claim 80, wherein the linked pluralities of rapamycin
2 have from 7 to 5×10^4 molecules linked.

1 83. A method as in any of claim 78, wherein the linked pluralities of
2 rapamycin are linked via attachment to a backbone.

1 84. A method as in claim 83, wherein the molecules comprise rapamycin
2 molecules which have been derivatized with linking moieties and wherein the rapamycin
3 molecules are covalently bound through the moieties to the backbone.

1 85. A method as claim 84, wherein the linking moieties are bound to the
2 rapamycin molecules at sites which do not sterically interfere with the active sites of
3 rapamycin so that rapamycin retains its activity when attached to the backbone.

1 86. A method as in claim 84, wherein the linking moieties are bound to
2 rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so
3 that rapamycin activity is inhibited while the rapamycin remains attached to the backbone
4 and restored when the rapamycin is released from the backbone.

1 87. A method as in claim 83, wherein the backbone degrades under
2 preselected conditions to release the rapamycin molecules.

1 88. A method as in claim 83, wherein the linking moieties lyse under
2 preselected conditions to replace the rapamycin molecules from the backbone.

1 89. A method as in claim 83, wherein the backbone comprises a poly
2 (amino acid).

1 90. A method as in claim 89, wherein the backbone is polyaspartate,
2 wherein rapamycin is covalently attached via an ester linkage between a free carboxylic acid
3 on the aspartate side chain to a free hydroxyl at position 42 of rapamycin.

1 91. A method as in claim 89, wherein the backbone is polylysine, wherein
2 rapamycin is covalently attached via a heterobifunctional linker between a free thiol on the
3 lysine to a free hydroxyl at position 42 of rapamycin.

1 92. A method as in claim 89, wherein the backbone is polylysine, wherein
2 rapamycin is covalently attached via an amide-ester linkage between a free amine on the
3 lysine to a free hydroxyl at position 42 of rapamycin.

1 93. A method as in claim 89, wherein the backbone is polylysine, wherein
2 rapamycin is covalently attached via a disulfide linkage through a free thiol introduced to the
3 rapamycin.

1 94. A method as in claim 83, wherein the backbone comprises
2 polyethylene glycol (PEG), wherein the molecules comprise rapamycin attached to the PEG
3 by ester linkages between free hydroxyls on the PEG and on the rapamycin.

1 95. A method as in any of claim 78, wherein the molecules are
2 polymerized.

1 96. A method as in claim 95, wherein the molecules comprise rapamycin
2 molecules which have been derivatized with linking moieties and wherein the rapamycin
3 molecules are polymerized through the linking moieties.

1 97. A method as in claim 96, wherein the linking moieties are bound to the
2 rapamycin molecules at sites which do not sterically interfere with the active sites of
3 rapamycin so that rapamycin retains its activity when polymerized.

1 98. A method as in claim 96, wherein the linking moieties are bound to the
2 rapamycin molecules at sites which sterically interfere with the active sites of rapamycin so
3 that rapamycin activity is inhibited while the rapamycin remains polymerized and restored
4 when the rapamycin is released.

1 99. A method as in claim 96, wherein the linking moieties lyse under
2 preselected conditions.

1 100. A method as in claim 96, wherein the linking moieties comprise
2 ascorbic acid attached to the rapamycin molecules via an ester linkage.

1 101. A composition as in any of claim 1, further comprising an unlinked
2 ascorbic acid moiety.